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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Jani et al.

Serial Number: 154,514

Filed: February 5, 1988

Group Art Unit: 125

Examiner: Douglas W. Robinson

FOR: SUSTAINED RELEASE COMFORT FORMULATION FOR GLAUCOMA THERAPY

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Larry A. Bruce, hereby declare and say as follows:

1. I received my B.S. in Chemistry/Biology from Mars Hill College in 1964. In 1968 I received my M.S. in physiology and in 1972 my Ph.D. in physiology/pharmacology from the University of Georgia. From September 1972 through August 1974 I was a post doctoral fellow in the Department of Physiology (Gastroenterology), University of Texas Health Science Center, Dallas, Texas. Following my post doctoral studies I was an assistant professor at the University of Texas Health Science Center in the Physiology Department. My major research interest was autonomic pharmacology. My teaching responsibilities included autonomic, cardiovascular, pulmonary, gastrointestinal and renal pharmacology/physiology. I worked for five years (March 1981 - May 1986) as a clinical scientist at Alcon Laboratories, Inc. (Alcon) in new product research for glaucoma. Two glaucoma products were developed from my unit during this time frame; Betoptic^{R} and Pilopine H.S. Gel^{R}. From June 1986 through February 1988 I was the Assistant Director of clinical ophthalmology at Alcon at which time I was responsible for,

among other things, planning and overseeing human clinical trials under United States Food and Drug Administration ("FDA") guidelines, particularly in the area of topical ophthalmic formulations, including formulations for the treatment of glaucoma.

2. I am currently the Assistant Director, Clinical Science, Head of Worldwide Product Support at Alcon in Fort Worth, Texas. My responsibilities include designing and implementing clinical studies worldwide for products recently approved by the FDA and/or equivalent agencies in other countries.

3. As a result of my educational and work-related experience I am generally knowledgeable with respect to the technology and literature relating to the use of ophthalmic pharmaceutical compositions, such as sustained release compositions for controlling and lowering intraocular pressure ("IOP") and methods for their use.

4. I am familiar with the Specification of U.S. Patent Application Serial No. 154,514 ("Application"), and understand that this Application sets forth claims to sustained release ophthalmic compositions comprising a beta-blocker or other IOP lowering drugs, an anionic mucomimetic polymer and a cation exchange resin, as well as methods for controlling and lowering IOP using the sustained release compositions.

5. As part of my responsibilities at Alcon, I have reviewed preclinical studies and supervised human clinical studies relative to the bioavailability, efficacy and comfort of topical ophthalmic compositions of the type described in the Application and I am familiar with the data resulting from both the preclinical and human clinical studies.

6. Preclinical, in vivo, bioequivalent studies were conducted at Alcon comparing the amount of betaxolol found in the aqueous humor of rabbits, some of which were treated with a commercially available 0.5%

betaxolol solution (i.e. BETOPTIC^{R}) and some of which were administered a 0.25% betaxolol suspension covered by the claims of the Application. The formula of the 0.5% solution and the 0.25% suspension are set forth below:

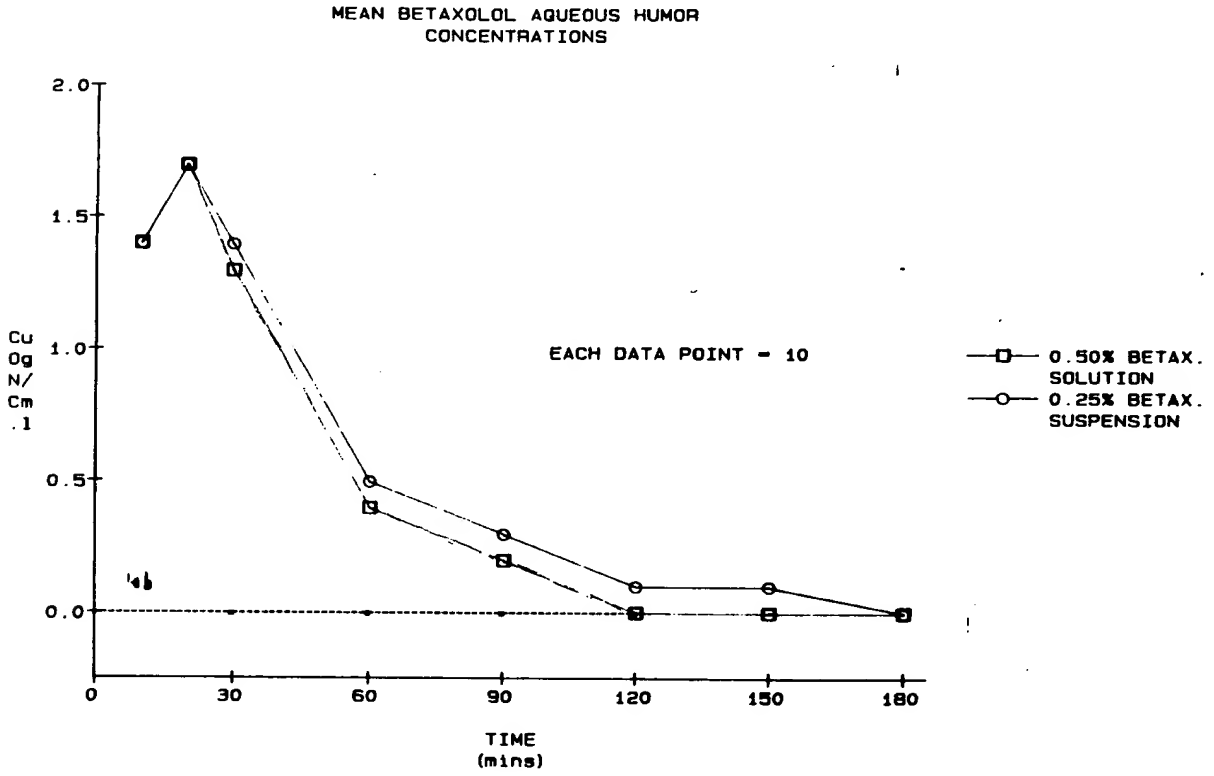
0.25% SUSPENSION

Ingredient	Percent w/v
Betaxolol hydrochloride	0.28 + 5% Excess (equivalent to 0.25 betaxolol base)
Poly(styrene-divinyl benzene) sulfonic acid (Amberlite^{R} IRP-69 Hydrogen form)	0.25
Carbomer, 934, NF	0.20
Edetate disodium, USP	0.01
Mannitol, USP	4.50
Benzalkonium chloride, as solution, NF	0.01 + 10% Excess
Hydrochloric acid, NF and/or sodium hydroxide, NF	Q.S. pH 7.6
Purified water	Q.S. 100

0.5% SOLUTION

Ingredient	Percent w/v
Betaxolol hydrochloride	5.6 + 2% Excess (equivalent to 5.0 betaxolol base)
Benzalkonium chloride	0.01% + 5% Excess
EDTA	0.01
NaCl	0.8
HCl/NaOH	Adjust to pH 7.1 - 7.7
Purified water	Q.S. (480ml)

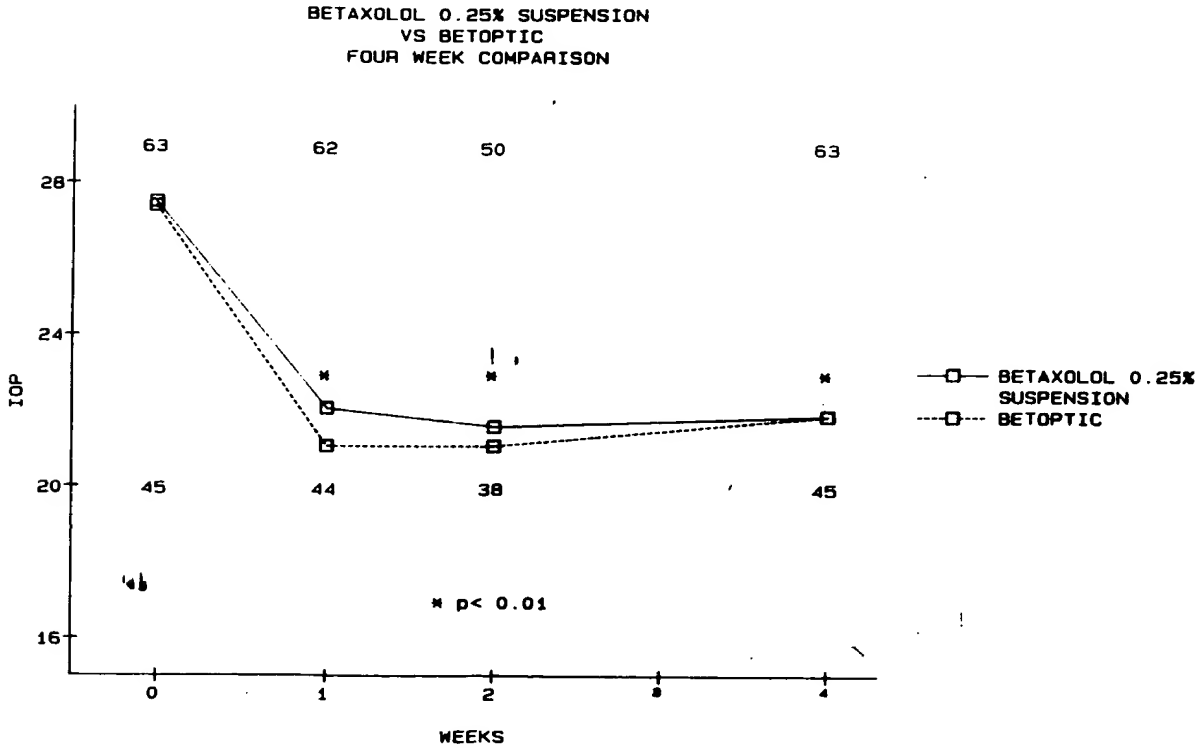
A total of 160 New Zealand rabbits were assigned to one of 16 groups. Eighty rabbits were dosed in both eyes with 30 microliters of the 0.5% solution and eighty with the 0.25% suspension. The rabbits were sacrificed at periodic intervals from 10 to 180 minutes. At each interval 5 rabbits dosed with the 0.5% solution and 5 dosed with the 0.25% suspension were sacrificed. Aqueous humor was removed from each eye of one animal and combined prior to analysis. All samples were assayed for betaxolol by high performance liquid chromatography. The results can be seen on the graph below entitled "Mean Betaxolol Aqueous Humor Concentrations."



The results demonstrate that Betaxolol was rapidly absorbed into the aqueous humor following topical administration of both formulations. Aqueous humor concentrations of 1.4 micrograms/ml were observed at 10 minutes for both formulations and a peak concentration of 1.7 micrograms/ml was achieved at 20 minutes for both formulations. The

mean concentration versus time profiles for the two treatments were closely matched such that an analysis of variance for data obtained at each sampling time through 90 minutes revealed no significant difference at $p < 0.05$. These data indicate that the 0.25% suspension provides for aqueous humor betaxolol concentrations essentially equivalent to the 0.5% solution. One can conclude that the polymer/resin used in the 0.25% suspension has provided for sustained release of the betaxolol in those rabbits dosed with the suspension.

7. In further support of the conclusion stated in paragraph 6, that the polymer/resin component of the claimed compositions provides for sustained release of betaxolol, a clinical study in which the intraocular pressures of human glaucoma patients dosed with the 0.25% suspension were compared with those of patients dosed with the 0.5% solution. Data collected from this comparative study is presented in the graph below entitled "Betaxolol 0.25% Suspension vs. Betoptic Four Week Comparison."



A total of 108 patients participated in this clinical study, 45 of which were treated with the 0.5% solution and 63 of which were treated with the 0.25% suspension. The average IOP values for each group at 1, 2 and 4 weeks were significantly reduced; and the average IOP values for each group were not statistically different from each other at the respective measurement times. One can conclude that, due to the sustained release properties of the 0.25% suspension, it is possible to reduce the concentration of betaxolol by one-half and still effectively control IOP.

8. Clinical studies conducted with human patients suffering from primary open angle glaucoma have been and are being conducted through Alcon under guidelines of the FDA [NDA 19-845, Betaxolol IND 17-568 (Protocols C-86-64; C-87-86; and C-86-24)]. These clinical studies are primarily directed to the safety and effectiveness of the above-identified 0.25% betaxolol suspension. Each of these studies includes a subjective evaluation of the discomfort experienced by the patients with the formulations tested. For a total of 305 patients involved in the three studies, 7.9% reported discomfort. Furthermore, in the study conducted according to protocol C-86-64, which is an ongoing, long-term study including 110 patients, only one (a little more than 1.0%) of the 94 who have completed 6 months of the two-year study has reported discomfort. In prior clinical studies with the 0.5% betaxolol solution, the results of which are reported in the attached Package Insert for BETOPTIC^{R} (Exhibit 1), 1 in 4 patients (25%) experienced discomfort on administration of the solution. Therefore, the incidence of discomfort with the 0.25% betaxolol suspension is significantly less than that seen with the 0.5% betaxolol solution.

9. As a result of the preclinical and completed and ongoing clinical studies discussed herein, it is my opinion that the compositions of the claimed invention provide substantial advantages to glaucoma patients whose IOP must be controlled. In particular, the compositions are not only effective in controlling IOP, but are significantly more comfortable on instillation. Thus, in an area where

poor patient compliance is a problem due to the age of most glaucoma patients (average age over 60 years), the significant improvement of yet another factor (stinging and its associated discomforts) which further contributes to poor patient compliance, is a significant finding.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information of belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent thereon.

Larry A. Bruce, Ph.D.

3-14-89
Date